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Use of pooled samples to assess human exposure to parabens, benzophenone-3 and triclosan in Queensland, Australia

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Abstract

Parabens, benzophenone-3 and triclosan are common ingredients used as preservatives, ultraviolet radiation filters and antimicrobial agents, respectively. Human exposure occurs through consumption of processed food and use of cosmetics and consumer products. The aim of this study was to provide a preliminary characterisation of exposure to selected personal care product chemicals in the general Australian population. De-identified urine specimens stratified by age and sex were obtained from a community-based pathology laboratory and pooled ($n = 24$ pools of 100). Concentrations of free and total (sum of free plus conjugated) species of methyl, ethyl, propyl and butyl paraben, benzophenone-3 and triclosan were quantified using isotope dilution tandem mass spectrometry; with geometric means 232, 33.5, 60.6, 4.32, 61.5 and 87.7 ng/mL, respectively. Age was inversely associated with paraben concentration, and females had concentrations approximately two times higher than males. Total paraben and benzophenone-3 concentrations are significantly higher than reported worldwide, and the average triclosan concentration was more than one order of magnitude higher than in many other populations. This study provides the first data on exposure of the general Australian population to a range of common personal care product chemical ingredients, which appears to be prevalent and warrants further investigation.

Keywords

Biomonitoring; Urine; Parabens; Personal care products; Population monitoring; Children

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The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2015.09.001>.

1. Introduction

The type, concentration and use of chemical ingredients in personal care products are many and varied. Parabens are alkyl esters (e.g., methyl (MeP), ethyl (EtP), propyl (PrP), butyl (BuP)) of p-hydroxybenzoic acid, used widely as antimicrobial preservatives in cosmetics, pharmaceuticals and processed food products (Eriksson et al., 2008; Shen et al., 2007; Soni et al., 2005) due to their stability, high water solubility, and low cost. Exposure occurs primarily via dermal absorption (Soni et al., 2005) and after metabolism, excretion occurs largely via urine. Results from in vitro and in vivo experiments suggest estrogenic activity of MeP, EtP, PrP and BuP (Boberg et al., 2010; Darbre and Harvey, 2008), but several orders of magnitude lower than that of oestrogen. Adverse reproductive effects of BuP and PrP have been reported in some animal studies (Oishi, 2002a,b) but not others (Hoberman et al., 2008), with some association with sperm damage (Meeker et al., 2011) and altered thyroid hormones (Koeppel et al., 2013) in humans.

Benzophenone-3 is a broadband ultraviolet radiation filter used as a sunscreen and photostabiliser in various cosmetic products worldwide; dermal contact is the dominant exposure pathway (Kim and Choi, 2014; Liao and Kannan, 2014). Urinary benzophenone-3 is used as the primary biomarker of exposure (Wang and Kannan, 2013). Benzophenone-3 exhibits slight estrogenic potential, and there is evidence for influence on reproduction and sex hormone signalling in rodents (Kim and Choi, 2014), and for influence on hormone-dependent diseases and adverse birth outcomes in humans (Kunisue et al., 2012; Wolff et al., 2008).

Triclosan is a synthetic, broad spectrum antimicrobial agent used in a wide range of personal care products and other consumer items (Rodricks et al., 2010; Witorsch and Thomas, 2010), and exposure mainly occurs through dermal application or oral use of consumer products containing triclosan. Triclosan is rapidly metabolised and excreted as conjugated urinary metabolites. The endocrine disrupting potential of triclosan is under debate (Huang et al., 2014; Jung et al., 2012; Lee et al., 2014; Witorsch, 2014; Witorsch and Thomas, 2010), and recent evidence suggests liver carcinogenicity (Yueh et al., 2014). Furthermore, concern has been raised as to the development of triclosan-resistant pathogens due to widespread use (Aiello and Larson, 2003; Levy, 2001).

Human exposure to chemicals used in personal care products occurs as a result of the frequent and complex use of such products, and biomonitoring is regarded as the gold standard for exposure assessment (Sexton et al., 2004). Biomonitoring data of the prevalence of exposures to chemicals used in personal care products exists for Northern European (Den Hond et al., 2013; Dewalque et al., 2014; Frederiksen et al., 2014; Moos et al., 2014; Pirard et al., 2012), North American (Calafat et al., 2008a,b, 2010; CDC, 2015, Health Canada, 2013; Meeker et al., 2013; Wang et al., 2013) and South East Asian (Kim et al., 2011; Ma et al., 2013; Shirai et al., 2013) populations, but the extent of Australians' exposure to personal care product chemicals is unknown. As biomonitoring is expensive pooling is an affordable alternative. The suitability of pooled biological samples for monitoring temporal and spatial trends in exposure has been demonstrated (Heffernan et al., 2013, 2014a,b). The aim of this

study was to provide a preliminary characterisation of exposure to selected personal care product chemicals in the general Australian population using pooled urine specimens.

2. Materials and methods

2.1. Study population and sample collection

De-identified urine specimens were obtained from a community-based pathology laboratory (Sullivan Nicolaides Pathology, Taringa, QLD, Australia) from surplus stored urine that had been collected and analysed as part of routine testing throughout the state of Queensland, Australia. Urine specimens were collected from November 2012 to November 2013 in sterile polyethylene urine specimen containers, refrigerated for up to three days, and then frozen. As this was a pre-existing, convenience population no specific sampling protocols were employed. This work was approved by the University of Queensland ethics committee (approval number 2013000397). The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

2.2. Pooling protocol

Descriptive information about each specimen was limited to date of sample collection, sex, and date of birth of the individual. Before pooling, samples were stratified by age and sex into the following strata: 0–4, 5–14, 15–29, 30–44, 45–59, >60 years. The mean age of each pool was calculated from the average age of the individuals making up that pool. A total of 2400 individual specimens were combined into 24 pools, with 100 individual specimens contributing to each pool; there was a replicate pool for each of the 12 demographic groups. Specimens were pooled based on volume, where each individual in the pool contributed the same volume, thus the concentration measured in each pool is equivalent to the arithmetic mean of the concentration in each individual sample contributing to the pool (Caudill, 2010; Mary-Huard, 2007). During pooling, individual urine specimens were thawed, homogenised and aliquoted, after which the pooled sample was well-mixed, divided into smaller aliquots and frozen until analysis. A synthetic urine sample was included as a procedural blank (Calafat and Needham, 2009). No measures of creatinine or specific gravity were available for individual samples.

2.3. Chemical analysis

Concentrations of the free and total (sum of free and conjugated) species of MeP, EtP, PrP and BuP and benzophenone-3 and triclosan in urine were measured at the CDC (Atlanta, USA) using online solid phase extraction-high performance liquid chromatography isotope dilution tandem mass spectrometry as described previously (Ye et al., 2005,2006). Concentrations of free species were measured using the same methodology, but omitting the enzymatic hydrolysis. To monitor for accuracy and precision, each analytical run included calibration standards, reagent blanks, and quality control materials of high and low concentrations. The limits of detection (LOD) were 1 ng/mL (MeP, EtP, triclosan), 0.2 ng/mL (benzophenone-3), and 0.1 ng/mL (PrP and BuP). We did not detect the target compounds in the synthetic urine sample.

2.4. Statistical analysis

The influence of age (in years) and sex on chemical concentration was assessed via linear regression on ln-transformed urinary concentration, as follows:

$$\text{Ln}(\text{concentration}) = I + \beta_1 * \text{Age} + \beta_2 * \text{Sex}. \quad (1)$$

An interaction term between age and sex was included in the models where significant. We summed the concentrations of the four parabens to create a summary measure (Σ paraben). All analyses were conducted using IBM SPSS Statistics, version 22 for Windows, (IBM, New York, USA, www.ibm.com). Criteria for significance were set as $p < 0.05$. Outliers in the ln-transformed values were identified using the outlier labelling rule (Hoaglin and Iglewicz, 1987; Hoaglin et al., 1986).

3. Results

3.1. Parabens

Results for MeP, EtP, PrP, BuP and Σ paraben concentrations for samples pooled by age and sex ($n = 24$) are summarised in Table 1. MeP, EtP, PrP and BuP were detected in all samples predominantly in their conjugated form (78–100%, Table SI-1) at total concentrations ranging from 74.4–1180, 6.3–802, 10.2–530 and 0.8–227 ng/mL, respectively; geometric means (GM) were 232 ng/mL (MeP), 33.5 ng/mL (EtP), 60.6 ng/mL (PrP), and 4.3 ng/mL (BuP). Σ paraben total concentration ranged from 114 to 1650 ng/mL, with GM 356 ng/mL. One pooled sample (pool 10, Table 1) had relatively high total concentrations of EtP (802 ng/mL), PrP (530 ng/mL) and BuP (227 ng/mL) compared with other pools in the same age strata. These values were identified as statistical outliers for EtP and BuP, but not for PrP. Omission of the outliers yields GMs of 29.1 ng/mL and 3.64 ng/mL for EtP and BuP, respectively..

There was a small but significant inverse association between age and total concentration for MeP ($p = 0.0001$), EtP ($p = 0.008$) and PrP ($p = 0.0004$), but not BuP (Table 2). When the outlier was removed, the strength of the association increased, and age became a significant predictor of BuP concentration ($p = 0.007$) (Table SI-2). Female pools had MeP total concentrations 1.8 times higher than male pools. There were no significant differences between male and female pools for EtP and PrP. For BuP sex was significant only if the outlier was omitted, with total concentrations in the female pools being 2.3 times higher than in male pools.

3.2. Benzophenone-3 and triclosan

Benzophenone-3 was detected in all pooled samples; total concentrations ranged from 16.5 ng/mL to 312 ng/mL (GM = 61.5 ng/mL) across all strata (Table 1). There was a significant interaction between age and sex in the multivariate model ($p = 0.007$, Table SI-3), with the highest total concentrations found in older females' pools. When the male and female data were examined separately, there was a small effect of age on concentration for female pools ($p = 0.019$) but not for male pools.

Triclosan was detected in all samples at total concentrations ranging from 24.1 ng/mL to 205 ng/mL (GM = 87.7 ng/mL, Table 1). Triclosan was not linearly associated with age (Fig. 1), with the highest total concentrations (100–205 ng/mL) found in the 15–29 years age strata pools. There were no significant differences between male and female pools.

4. Discussion

4.1. Parabens

Paraben total concentration was inversely associated with age, with a significant decrease across strata from 0 to 4 to 15–29 years (Fig. 1), followed by a plateau from 16 to >60 years for MeP, EtP and PrP (BuP did not appear to follow this trend). Total concentrations of MeP and PrP were higher than EtP and BuP across all age strata (Table 1), consistent with the more prevalent use of MeP and PrP in personal care products and food processing (Shen et al., 2007; Soni et al., 2005; Wang and Zhou, 2013). The highest MeP and PrP total concentrations were found in pools from children aged 5–14 years (Fig. 1) at GM552 and 107 ng/mL, respectively. These concentrations were substantially higher than GMs of MeP and PrP, respectively, in children from China (9–10 years, $n = 70$, 5.28 and 1.89 ng/mL) (Wang et al., 2013), Belgium (1–6 years, $n = 23$, median = 34.8 and 2.1 ng/mL) (Dewalque et al., 2014), India (2–14 years, $n = 76$, 6.77 and 0.86 ng/mL) (Xue et al., 2015) and the USA (3–10 years, $n = 40$, 62.4 and 0.92 ng/mL (Wang and Kannan, 2013) and 6–11 years, $n = 415$, 33.9 and 3.28 ng/mL (CDC, 2015). Similarly, GM total concentrations in these general Australian population pools were higher than adult populations in the USA (CDC, 2015), China (Wang et al., 2013), Belgium (Dewalque et al., 2014), Denmark (Frederiksen et al., 2011) and Greece (Asimakopoulos et al., 2014) (Table SI-4). Urinary total concentrations for MeP, PrP and BuP were approximately two times higher in female pools than in male pools (Table 2). This sex-related difference in paraben concentrations has also been reported in the US general population (Calafat et al., 2010; CDC, 2015), and is likely reflective of the more frequent use of paraben-containing cosmetic products by women than men. There was no significant interaction between age and sex for any parabens.

The age trend with paraben total concentration is clear, particularly for MeP and PrP, and is suggestive of higher exposures to parabens in Australian children than in adults. This may be the result of behavioural or physiological differences between children and adults, such as mouthing behaviours (Tulve et al., 2002; Xue et al., 2007); a larger surface area-to-bodyweight ratio, increasing the potential for exposure via dermal absorption; increased ventilation rate relative to lung surface area for greater exposure via inhalation; or increased energy and water intake combined with enhanced retention and absorption of nutrients for increased exposure via food (Miller et al., 2002; WHO, 2011). The opposite relationship is observed in the United States, where adults have higher paraben concentrations than children (CDC, 2015), suggesting that the observed age trend in the Australian population is most likely due to child-specific exposure sources such as baby products (wipes, lotions etc.). Although this was a convenience population and no specific sampling strategies were employed, the fact that the parabens were measured predominantly in their conjugated form (78–100%, Table SI-1) rules out systematic exogenous contamination of the samples with the target parabens.

4.2. Benzophenone-3

Benzophenone-3 was associated with age for females, but not for males in the general Australian pools. Increased total concentrations of benzophenone-3 in older females is most likely from frequent sunscreen use, and consistent with the generally more positive attitude towards skin care in females than in males, and in adults compared with adolescents (Abroms et al., 2003; Manová et al., 2013; Potente et al., 2011). This trend was observed in the NHANES 2009–10 population, where adult females had GM concentrations more than double those of males (CDC, 2015), but this is not seen in all studies (Chen et al., 2012; Gao et al., 2015; Zhang et al., 2013). Benzophenone-3 concentrations were similar in both sexes for school aged children (<15 years, Fig. 1), and may be the result of “SunSmart” sun safety policies in place in Australian schools, where sunscreen application is mandatory (Montague et al., 2001; Shih et al., 2009).

A recent review by Kim and Choi (2014) summarises human biomonitoring results for benzophenone-3 in urine. The Australian population pools showed substantially higher urinary concentrations (GM 61.5 ng/mL) than adult populations in China (GM: 0.62, $n = 106$) (Gao et al., 2015); Denmark (GM 1.73–4.25, $n = 1003$) (Frederiksen et al., 2014); France (median: 1.3 ng/mL, $n = 191$) (Philippat et al., 2012); Spain (median: 3.4 ng/mL, $n = 120$) (Casas et al., 2011); and the USA (GM 23.3 ng/mL, $n = 2749$ (CDC, 2015) and 6.1 ng/mL, $n = 625$ (Kunisue et al., 2012), respectively). Similarly, concentrations in Australian children (pool mean 17.2–96.2 ng/mL, $n = 8$ pools, 0–14 years) were considerably higher than in children from India (GM: 0.91 ng/mL, $n = 76$, 2–14 years) (Xue et al., 2015) and China (GM: 9.97 ng/mL, $n = 38$, 3–10 years) (Wang and Kannan, 2013) (Table SI-4), which may be attributed to lower sunscreen usage in India and China compared to Australia. Results orders of magnitude higher (>2 mg/mL) than reported in our study have been reported in some studies (Calafat et al., 2008a; Wolff et al., 2008), but pooled samples are unable to capture this variance. Of note, Australia and New Zealand have the highest rate of skin cancer in the world, approximately 12 times the global average (Cancer Australia, 2008; Ferlay et al., 2013). The significantly higher mean benzophenone-3 total concentrations in the Australian pools across the population compared to other countries globally is most likely reflective of the frequent sun safety public health campaigns and much higher sunscreen use in Australia. Further, samples were collected from Queensland, Australia, colloquially referred to as the ‘Sunshine State’. Located in the North East of Australia, Queensland has the highest average maximum temperatures of any state and the highest rate of skin cancers in Australia, and thus, in the world (AACR, 2012). The combination of these factors means that one would expect considerable sunscreen use and thus greater benzophenone-3 concentrations in residents of Queensland than in other Australian states. Similar regional variability has been reported in the USA, with significantly higher benzophenone-3 levels in women from California than those from Utah (Kunisue et al., 2012). Consequently, the benzophenone-3 results from the present study may not be representative of average Australians' exposure considering climate and average sun exposure.

4.3. Triclosan

Exposure of the Australian population to triclosan has previously been demonstrated using blood (Allmyr et al., 2008) and breast milk (Toms et al., 2011), but not urine. The highest urinary total concentrations of triclosan were found in females aged 16–45 years (pool means ranging from 104 to 205 ng/mL), and may be the result of increased use of antibacterial products among this demographic. Similarly, Den Hond et al. (2013) report higher triclosan levels in 14–15 year old Flemish adolescent females compared with males, but in NHANES there was no significant differences between US males and females (CDC, 2015). In the present study there was no association between urinary triclosan and age or sex, and these variables accounted for only 1% of the observed variance, consistent with a previous Australian study of individual human milk samples showing high variability in triclosan concentrations (Toms et al., 2011). This suggests that there are factors other than age and sex that contribute to measured triclosan concentrations, most likely exposure source - specifically the type and frequency of triclosan-containing products (e.g. personal care products and consumer products treated with antimicrobials, such as socks and kitchenware (Adolfsson-Erici et al., 2002)) used by a given individual. For example, in a study of Flemish adolescents triclosan levels were associated with the use of day/night cream and haircare products (Den Hond et al., 2013), and the use of liquid soap was significantly associated with triclosan levels in Puerto Rican pregnant women (Meeker et al., 2013).

The average triclosan total concentration in these Australian pools (pool mean: 83.0 ng/mL) was more than one order of magnitude higher than those reported in Flemish adolescents (GM 2.19 ng/mL, $n = 193$) (Den Hond et al., 2013), and adults from the Korean National Human Biomonitoring (GM 1.68 ng/mL, $n = 1860$) (Kim et al., 2011); and significantly higher than concentrations in Greece (GM 8.0 ng/mL, $n = 100$) (Asimakopoulos et al., 2014), the United States 2009–10 NHANES (14.5 ng/mL, $n = 2749$) (CDC, 2015), and pregnant women from Puerto Rico (GM 29.9 ng/mL, $n = 105$) (Meeker et al., 2013) and several of the continental United States and Hawaii (GM 19.0 ng/mL, $n = 506$) (Mortensen et al., 2014) (Table SI-4). Triclosan urinary total concentrations in the Australian pools were comparable to those found in Danish mothers (GM 66 ng/mL, $n = 145$) and children (GM 43 ng/mL, $n = 143$) (Frederiksen et al., 2013b).

4.4. Limitations

A number of assumptions have been made that must be considered when interpreting the results of the study: (1) pathology specimens do not introduce significant bias into the study population; (2) pooled samples provide an accurate measurement of mean concentration; and (3) spot samples provide a reasonable estimate of internal exposure over a given time frame.

4.4.1. The use of pooled, pathology specimens—The study population consisted of convenience samples collected during the course of routine pathology testing. The samples are not statistically representative of the Australian population as a whole, but there is no reason to expect exposures to the target analytes to be different in this community pathology-sourced population than in the general Australian population (except perhaps for

benzophenone-3 and this would be largely related to the geographical location of the community pathology laboratory). The use of pooled specimens is advantageous as it saves significantly on analytical costs, reduces the time and resources required for recruitment, and may avoid ethical difficulties associated with reporting individual results (reviewed in Heffernan et al. (2014b)). Pooled pathology specimens were used successfully in previous studies to measure urinary bisphenol A, another ubiquitous short half-life environmental chemical (Heffernan et al., 2013,2014a). As discussed above, because this was a pre-existing, convenience population no specific sampling protocols were employed. This includes strategies related to sample collection containers and protocol, and sample storage. However, synthetic urine was collected, stored and processed under conditions simulating real sample conditions with all results <LOD, and all of the target analytes were measured predominately in their conjugated form. Together these findings suggest that there was no systematic contamination resulting from the sampling and pooling protocols. No creatinine or specific gravity data were available for the samples used in this study. However, for the interpretation of pooled measurements as representative measures of average concentration, variation in individual sample hydration status is expected to be averaged out and not introduce significant bias to the estimated average concentrations and excretion rates.

4.4.2. Variability in short half-life chemicals and the use of spot samples—For mainly episodic exposures to short half-life chemicals with rapid elimination kinetics, a large degree of within- individual variability is expected (Aylward et al., 2012), sometimes up to 3 orders of magnitude (Koch et al., 2014; Preau et al., 2010), and thus the time of sample collection relative to the exposure event will strongly impact the urinary concentration for any given person. Intraclass correlation coefficients (ICCs) for benzophenone-3 (0.57–0.81), triclosan (0.55–0.93) and EtP (0.48–0.76) (Koch et al., 2014; Lassen et al., 2013; Philippat et al., 2013) suggest that a spot sample provides a reasonable estimate of urinary concentration over days to months. For MeP and PrP ICCs are lower (0.2–0.56 and 0.29–0.51, respectively) (Engel et al., 2014; Koch et al., 2014; Meeker et al., 2013; Philippat et al., 2013; Smith et al., 2012) and thus measurements have higher uncertainty. The use of pooled samples is likely to mitigate this effect to some extent, as persons having extreme high or low concentrations will be averaged out by the large number of individuals contributing to the pool.

This study provides the first data on exposure among the general Australia population to a range of common personal care product chemical ingredients. Parabens and triclosan total concentrations in these pooled samples are significantly higher than the concentrations reported in similar populations worldwide, and age was a significantly inversely associated with paraben concentration. Benzophenone-3 total concentrations were significantly higher than reported values elsewhere, likely reflective of the prevalent sunscreen use in Australia; but may be elevated in Queensland compared with other Australian states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MeP	methyl paraben
EtP	ethyl paraben
PrP	propyl paraben
BuP	butyl paraben
CDC	Centers for Disease Control and Prevention, United States
LOD	limit of detection
ng/mL	nanograms per millilitre
GM	geometric mean
NHANES	National Health and Nutritional Examination Survey
ICC	intraclass correlation coefficient

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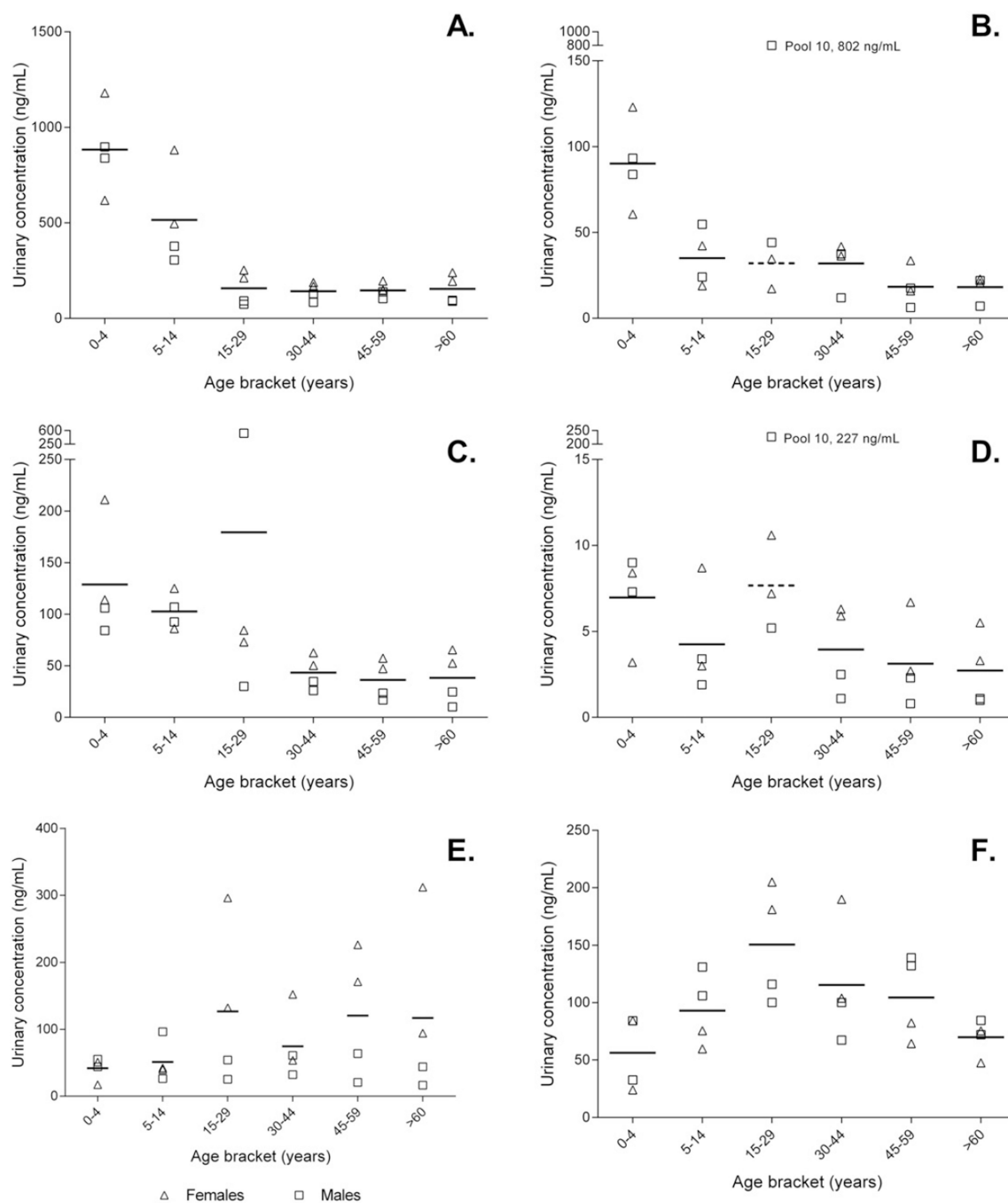
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**Fig. 1.**

Urinary total concentration (ng/mL) versus age (years) for methyl-, ethyl-, propyl- and butyl paraben; and benzophenone-3 and triclosan (A to F, respectively). Triangles denote female pools, squares denote male pools. Horizontal line indicates mean concentration of four pools in each age strata. Dashed horizontal line indicates mean concentration for age strata with outliers removed. Outliers labelled on ethyl- and butyl paraben plots.

Table 1

Summary of pool characteristics and chemical concentration (ng/mL) per strata. Each pool represents 100 individuals.

Pool #	Age strata (years)	Av. age (years)	Urinary total concentration (ng/mL)					
			Benzophenone-3	Triclosan	MeP	EtP	PrP	BuP
1	0-4	2.93	55.3	84.2	898	93.2	106	7.3
2		2.74	44.0	32.6	839	83.8	84.3	9
3		3.33	51.0	84.3	1180	123	211	8.4
4		3.24	17.2	24.1	618	60.6	114	3.2
5	5-14	8.83	26.2	106	306	24.1	92.5	1.9
6		9.21	96.2	131	378	54.8	107	3.4
7		8.74	39.8	75.5	882	18.9	125	8.7
8		9.54	42.3	59.8	496	42.3	86.1	3
9	15-29	24.3	54.1	116	74.4	44.2	30.1	5.2
10		24.0	25.3	100	91.9	802*	530	227*
11		24.0	132	205	253	34.6	84.5	10.6
12		23.4	296	181	212	17.2	73.1	7.2
13	30-44	37.8	32.2	100	129	12	34.8	2.5
14		37.3	60.9	67.4	84.6	37.5	26	1.1
15		36.7	152	190	188	41.8	62.6	6.3
16		36.8	53.6	104	168	36.3	50.4	5.9
17	45-59	52.9	20.7	139	139	17.5	17	0.8
18		53.2	63.7	132	104	6.3	23.6	2.3
19		53.3	226	82.3	196	33.6	57.4	6.7
20		53.0	171	64.4	149	15.9	47.2	2.7
21	>60	73.7	44.0	84.4	90.1	22	24.8	1.1
22		71.9	16.5	72.1	95.4	7.1	10.2	1
23		75.1	312	47.5	194	20.6	52.6	3.3
24		76.1	94.2	75.4	240	22.9	65.5	5.5
Total			61.5	87.7	232	33.5	60.6	4.32

Italicized data represent females pools. Asterisk indicates statistical outlier.

Table 2

Regression parameters (β (95% CI)) for log-transformed urinary total concentrations (ng/mL) of methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP), butyl paraben (BuP); and sum paraben (Σ paraben) (sum of MeP, EtP, PrP and BuP) ($n = 24$ pooled samples).

	MeP	EtP	PrP	BuP	Σ paraben
Intercept	6.499 (6.029 to 6.969)	4.198 (3.462 to 4.933)	5.076 (4.556 to 5.597)	2.262 (1.368 to 3.156)	6.861 (6.403 to 7.318)
Age (years)	-0.023 *** (-0.033 to -0.013)	-0.021 ** (-0.037 to -0.006)	-0.022 *** (-0.032 to -0.011)	-0.017 (0.035 to 0.001)	-0.024 *** (-0.033 to -0.014)
Sex	0.576 * (-1.056 to -0.097)	0.053 (-0.697 to 0.803)	-0.499 (-1.030 to 0.031)	-0.461 (-1.373 to 0.451)	-0.355 (-0.821 to 0.112)
R ²	0.589	0.291	0.503	0.184	0.585

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.